Protein-RNA Networks Regulated by Normal and ALS-Associated Mutant HNRNPA2B1 in the Nervous System.

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Public Summary:

Scientific Abstract:
HnRNPA2B1 encodes an RNA binding protein associated with neurodegeneration. However, its function in the nervous system is unclear. Transcriptome-wide crosslinking and immunoprecipitation in mouse spinal cord discover UAGG motifs enriched within approximately 2,500 hnRNP A2/B1 binding sites and an unexpected role for hnRNP A2/B1 in alternative polyadenylation. HnRNP A2/B1 loss results in alternative splicing (AS), including skipping of an exon in amyotrophic lateral sclerosis (ALS)-associated D-amino acid oxidase (DAO) that reduces D-serine metabolism. ALS-associated hnRNP A2/B1 D290V mutant patient fibroblasts and motor neurons differentiated from induced pluripotent stem cells (iPSC-MNs) demonstrate abnormal splicing changes, likely due to increased nuclear-insoluble hnRNP A2/B1. Mutant iPSC-MNs display decreased survival in long-term culture and exhibit hnRNP A2/B1 localization to cytoplasmic granules as well as exacerbated changes in gene expression and splicing upon cellular stress. Our findings provide a cellular resource and reveal RNA networks relevant to neurodegeneration, regulated by normal and mutant hnRNP A2/B1.